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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,096	GOLDSTEIN ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-61, 63-65 and 73-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-61, 63-65 and 73-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/17/05, 8/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The reply received 8/25/05 amending claims 49, 52, 53, 56-60, 63-65, 73, and 103 and canceling claims 62 and 110 is acknowledged. Claims 49-61, 63-65, and 73-109 are currently under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Prior art references can be found in a prior Office action, unless otherwise noted.

Specification

The objections to the specification are withdrawn in light of the amendments to the specification and the new title and abstract.

Claim Objections

The objections to the claims are withdrawn in light of the claim amendments.

Claim 52 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is not clear what additional limitations claim 52 imposes on the method of the parent claim, since irradiating tissue inherently forms irradiated tissue. Clarification is required.

Claim Rejections - 35 USC § 112

The rejections under 35 U.S.C. § 112, second paragraph, are withdrawn in light of the claim amendments and applicant's comments.

Claims 49-61, 63-65, and 73-109 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 49 recites a method of preparing a tissue "with reduced tissue damage" without providing a point of reference. "Reduced" is a relative term and, as such, is indefinite in the absence of a specific comparison. Clarification is required. Because claims 50-61, 63-65, and 73-109 depend from indefinite claim 49 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 102

The rejections under 35 U.S.C. § 102(b) are withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 103

Claims 49, 50, 52-61, 63-65, 73, 81-90, 98, 101-106, and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. taken in view of Freeman, Jr. The claims are drawn to a method substantially as described above. In some dependent claims, the cryopreserved tissue is irradiated with ionizing radiation, for example gamma radiation, after cryopreservation. In some dependent claims, a particular amount of radiation is used, for a particular time.

As discussed previously, Fisher et al. teach a method for cryopreserving liver slices in V-7 solution comprising combining liver slices with V-7 solution and lowering the temperature of the resulting combination to –196°C, a temperature at which the tissue is stable for years. Fisher et al. do not teach irradiating the tissue at any time.

Freeman, Jr. teaches a method for the sterilization of bovine tendons comprising irradiating said tendons with 2,000,000-5,000,000 rads of sterilizing high-energy gamma radiation from ^{60}Co decay (column 5, lines 13-24). Freeman, Jr. further suggests that an equivalent high-energy radiation source may be electron beam acceleration (column 4, lines 15-19). Freeman, Jr. further teaches that cross-linking tissue with, for example, glutaraldehyde prior to irradiation prevents degradation of proteins associated with gamma radiation (column 3, lines 30-38, and column 4, lines 34-68). Finally, Freeman et al. teach that tissue may be crosslinked, placed into physiological saline, and then irradiated (column 5, lines 13-17).

Freeman, Jr. does not recite or imply packaging, so it is silent as to whether irradiation should be carried out before or after any packaging of cryopreserved tissue; however, the order in which these steps are performed is clearly a matter of routine optimization. M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law... If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results.

A person of ordinary skill in the art would have had a reasonable expectation of success in sterilizing the cryopreserved tissue of Fisher et al. with the gamma-irradiation step of Freeman, Jr. because Freeman, Jr. teaches that gamma irradiation efficiently sterilizes tissue and tissue matrices (column 4, lines 20-26) and that said irradiation does not degrade the tissue so treated when the tissue has been crosslinked with glutaraldehyde (column 5, lines 18-24). The skilled artisan would have been motivated to use the irradiation step of Freeman, Jr. on the cryopreserved tissue of Fisher et al. for the expected benefit of preventing microbial infestation of said tissue, allowing it to be used later for transplantation procedures; in fact, Freeman, Jr. teaches that the irradiation process decreases the potential antigenicity of the treated tissue (column 4, lines 55-60). Freeman, Jr. also teaches that crosslinked, irradiated tissue is more flexible and less rigid than non-irradiated tissue (column 4, lines 40-48).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to treat the cryopreserved tissue of Fisher et al. with the glutaraldehyde cross-linking and gamma irradiation steps of Freeman, Jr. because Freeman, Jr. teaches that said steps provide so-treated tissue numerous benefits as they pertain to downstream applications.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the examiner provided no motivation to combine the aqueous preservation solution of Fisher with the glutaraldehyde crosslinking treatment of Freeman, Jr. (Remarks, page 30). Applicant further alleges that combining the

methods of Fisher et al. and Freeman, Jr. would result in "tissue that has been glutaraldehyde cross-linked and cryopreserved" (*ibid.*) These arguments have been fully considered, but they are not persuasive.

As discussed above, Freeman, Jr. teaches that tissue may be cross-linked with glutaraldehyde and then placed into physiological saline, where it is irradiated (column 5, lines 1-24). The V-7 solution of Fisher et al. is a physiological saline (Table 2). Clearly, combining cross-linked tissue and aqueous, physiological solutions is contemplated, even preferred, by Freeman, Jr.

The instantly claimed method **comprises** providing an aqueous preservation solution, combining said solution with a tissue, and lowering the temperature of the resulting mixture. The claim does not, however, specifically exclude embodiments in which the tissue is crosslinked prior to irradiation. The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Invitrogen Corp. v. Biocrest Mfg.*, L.P., 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003). The transition "comprising" in a method claim indicates that the claim is open-ended and allows for additional step. See M.P.E.P. § 2111.03. The claims therefore encompass methods comprising the recited steps and further comprising a cross-linking step.

According to the teachings of Freeman, Jr., some sort of cross-linking step or other protective step appears to be required in order to obtain a tissue with reduced tissue damage compared to non-crosslinked tissue. Freeman, Jr. specifically teach that

irradiation degrades proteins (column 3, lines 34-36). It is not clear that the claimed method would produce the recited outcome without cross-linking the tissue first, in light of the teachings of Freeman, Jr.

Claims 49-61, 63-65, and 73-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. taken in view of Freeman, Jr. as applied to claims 49, 50, 52-65, 73, 81-90, 98, 101-106, 108, and 110 above, and further in view of Carstairs et al. (1997, U.S. Patent 5,677,019; reference B), Demetriou et al. (2000, U.S. Patent 6,140,123; reference C), Lawrence et al. (1979, U.S. Patent 4,155,331; reference D), Chrisope (1994, U.S. Patent 5,279,964; reference E), and Malfroy-Camine et al. (1995, U.S. Patent 5,403,834; reference F). The claims are drawn to a method as described above. In some dependent claims, the bio-compatible buffer, cell-impermeant constituent, cell-permeant constituent, and radical scavenger are selected from a list and are each present in a particular concentration.

As detailed above, Fisher et al. teaches a method for cryopreserving liver slices in V-7 solution comprising combining liver slices with V-7 solution and lowering the temperature of the resulting combination to –196°C. Freeman, Jr. teaches a method for the sterilization of bovine tendons comprising crosslinking said tendons with glutaraldehyde and then irradiating said tendons with sterilizing high-energy gamma radiation. Neither Fisher et al. nor Freeman, Jr. addresses each and every embodiment for the bio-compatible buffer, cell-impermeant constituent, cell-permeant constituent, and radical scavenger recited in the dependent claims.

Carstairs et al. teach a method for preserving tissue comprising mixing the tissue with a preserving solution comprising propylene glycol, 1,4-butanediol, isopropanol, and water (Example 3).

Demetriou et al. teach cryopreservation using various bio-compatible buffers (column 7, lines 30-40), radical scavengers (column 7, lines 21-29), cryopreservatives (column 8, lines 1-12), and constituent salts (column 7, lines 4-11). Demetriou et al. further teach various embodiments of freezing protocols (column 8, line 66 through column 10, line 65).

Lawrence et al. teach that acceptable cryoprotectants include glycerol, glucose, fructose, DMSO, and polyvinylpyrrolidone (column 5, lines 20-27).

Chrisope teaches a cryoprotectant solution comprising carbohydrate (*e.g.* dextrose), a reducing agent (*i.e.* radical scavenger; sodium ascorbate), and a preservative (*i.e.* an alcohol, including isopropanol).

Malfroy-Camine et al. teach that radical scavengers (including tocopherol, ascorbate, glutathione, and N-acetylcysteine) enhance cryopreservation of cells, tissues, and organs by increasing the viability of recovered specimens (column 6, lines 7-39).

The selection of bio-compatible buffer, cell-impermeant constituent, cell-permeant constituent, and radical scavenger and the concentration of each in the claimed cryopreservation clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that the numerous bio-compatible buffers are functionally equivalent to each other, as are each of the cell-

impermeant constituents to each other, and so on. Absent a showing of unexpected results, the claimed embodiments merely recite various obvious modifications of cryopreservation solutions well known in the art. A holding of obviousness over the cited claims is therefore clearly required.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute any of the recited bio-compatible buffers, cell-impermeant constituents, cell-permeant constituents, and radical scavengers into the solution of Fisher et al. because Carstairs et al., Demetriou et al., Lawrence et al., Chrisope, and Malfroy-Camine et al. teach that these and other embodiments are art-accepted equivalents for each other.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that the teachings of Carstairs et al., Demetriou et al., Lawrence et al., Chrisope, and Malfroy-Camine et al. are too diverse to read on the instantly claimed invention (Remarks, pages 30-31). Applicants further allege that that none of the references teach the claimed order of steps. These arguments have been fully considered, but they are not persuasive.

First, Carstairs et al., Demetriou et al., Lawrence et al., Chrisope, and Malfroy-Camine et al. were cited as evidence that the recited species of claims 83, 93, 98, and 103 are art-accepted substitutes. The examiner does not dispute that Carstairs et al., Demetriou et al., Lawrence et al., Chrisope, and Malfroy-Camine et al. discuss preservation of diverse tissues and cells; indeed, the fact that the components of the

instantly claimed invention can be used on such a wide variety of cells and tissues lends support to the examiner's assertion that the recited species in claims 83, 93, 98, and 103 are art-accepted substitutes for each other.

With regard to the order of steps, M.P.E.P. § 2144 recites, "The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law... If the facts in a prior legal decision are sufficiently similar to those in an application under examination, the examiner may use the rationale used by the court." In *In re Burhans, 154 F.2d 690, 69 USPQ 330* (CCPA 1946), the court found that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results. In *In re Gibson, 39 F.2d 975, 5 USPQ 230* (CCPA 1930), the court found that selection of any order of mixing ingredients is *prima facie* obvious.

No claims are allowed. No claims are free of the art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SANDRA E. SAUCIER
PRIMARY EXAMINER

Lora E Barnhart

leb